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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte YVONNE M. GOERLACH-DOHT, JUERGEN HERMANNNS, and
NICHOLAS S. GRASMAN¹

Appeal 2014-009652
Application 13/156,889
Technology Center 1600

Before DEMETRA J. MILLS, FRANCISCO C. PRATS, and
JOHN E. SCHNEIDER, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134(a) involves claims to methods of controlling or adjusting the release of an active ingredient from a dosage form. The Examiner rejected the claims as anticipated and for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm in part.

STATEMENT OF THE CASE

Appellants' invention "relates to a method of controlling or adjusting release of an active ingredient from a dosage form comprising the active ingredient." Spec. 1. The Specification discloses that it is known in the art

¹ Appellants state that "real party of interest is Dow Global Technologies LLC, a wholly-owned subsidiary of The Dow Chemical Company." App. Br. 3.

that sustained release dosage forms may be prepared by milling or grinding a polysaccharide, such as hydroxypropyl methylcellulose, into small particles and incorporating the polysaccharide into the dosage form. *Id.* at 1–2.

“Surprisingly, it has been found that there is a correlation, typically a linear correlation, between the [liquid] diluent load of the polysaccharide derivative prior to dry-grinding and the percentage of active ingredient released over time from a dosage form comprising the active ingredient and the polysaccharide derivative.” *Id.* at 2–3. In particular, it has “surprisingly been found that a higher diluent load of the polysaccharide derivative prior to dry-grinding leads to a faster release of the active ingredient over time and vice versa.” *Id.* at 3.

More particularly, in its examples, the Specification discloses that by incorporating different predetermined amounts of water into the polysaccharide mixture prior to dry grinding the polysaccharide, there is a “correlation between the water load of the particulate polysaccharide derivative prior to dry-grinding and the controlled drug release performance using Ketoprofen which was determined after 3, 6, 12, and 20 hours.” *Id.* at 16.

Claim 1, the sole independent claim on appeal, and claim 3 are representative and read as follows (App. Br. 15):

1. A method of controlling or adjusting release of an active ingredient from a dosage form comprising the active ingredient and a polysaccharide derivative, which method comprises the steps of
 - a) providing a composition comprising a polysaccharide derivative and a controlled amount of a liquid diluent, based on the dry weight of the polysaccharide derivative,
 - b) subjecting the composition to a dry-grinding operation to provide a dry-ground polysaccharide derivative, and

- c) then combining the dry-ground polysaccharide derivative and an active ingredient, and incorporating them into a dosage form,

wherein the release of the active ingredient from the dosage form is controlled and adjusted by controlling and adjusting the amount of the liquid diluent, based on the dry weight of the polysaccharide derivative in step a), and wherein the polysaccharide derivative is selected from the group consisting of methyl cellulose, methyl hydroxyethyl cellulose, methyl hydroxypropyl cellulose and hydroxypropyl cellulose.

3. The method of claim 1 wherein the release of the active ingredient from the dosage form at a given time is adjusted to a first value by a first amount of the liquid diluent, based on the dry weight of the polysaccharide derivative in step a), and the release of the active ingredient from the dosage form at the given time is adjusted to a second value by a second amount of the liquid diluent, based on the dry weight of the polysaccharide derivative in step a).

The following rejections are before us for review:

(1) Claims 1, 3, 10, and 15, under 35 U.S.C. § 102(b), as anticipated by Schlesiger² (Final Action 3–4; Ans. 2–3);

(2) Claims 1, 3, 10, and 11, under 35 U.S.C. 103(a), for obviousness over Sugimoto³ (Final Action 5–7; Ans. 3–5);

(3) Claims 1 and 9, under 35 U.S.C. § 103(a), for obviousness over Schlesiger and Weber⁴ (Final Action 8; Ans. 5–6); and

² U.S. Patent No. 6,509,461 B2 (issued Jan. 21, 2003).

³ Masaaki Sugimoto et al., *Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel cogrinding method using water-soluble polymer*, 160 INT. J. PHARM. 11–19 (1998).

⁴ U.S. Patent No. 6,320,043 B1 (issued Nov. 20, 2001).

(4) Claims 1 and 16, under 35 U.S.C. § 103(a), for obviousness over either Sugimoto or Schlesiger in combination with Andrews⁵ (Final Action 9; Ans. 6–7).

ANTICIPATION—SCHLESIGER

The Examiner found that Schlesiger described a process, encompassed by claims 1, 3, 10, and 15, of preparing a composition containing a polysaccharide and an active ingredient, the process including the step of dry grinding the polysaccharide in the presence of a predetermined amount of diluent. Ans. 3. In particular, the Examiner found that the “relative amount of diluent to polysaccharide derivative is controlled and adjusted within predetermined limits.” *Id.* citing Schlesiger 5:59–64.

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

[T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .

After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

Appellants’ arguments do not persuade us that a preponderance of the evidence fails to support the Examiner’s *prima facie* case of anticipation as to representative claim 1.

As the Examiner found, and as required in steps (a) and (b) of Appellants’ claim 1, Schlesiger discloses a process in which a cellulose derivative encompassed by claim 1 is combined with a liquid diluent and then dry ground. *See, e.g.*, Schlesiger 11:38–12:18 (describing combination

⁵ U.S. Patent No. 2,262,155 (issued Nov. 11, 1941).

of methyl hydroxyethyl cellulose and 55 weight % water based on cellulose derivative content and then grinding in high rotational speed gas jet rotary mill).

As to the incorporation of the ground cellulose into a dosage form, recited in step (c) of claim 1, Schlesiger discloses that “active substances may optionally be added before, during or after one or more of the steps of the process, i.e., swelling or dissolution of the cellulose derivative in water, mill drying of the swollen or dissolved cellulose derivative, and drying of the finely particulate cellulose derivative.” *Id.* at 9:19–24. Schlesiger discloses that “[b]y the term active substances are understood to be substances that do not have any chemical effect on the cellulose derivative and that utilise the cellulose derivative as a binder. Typical active substances are . . . pharmaceuticals” *Id.* at 9:42–46.

As the Examiner found, Schlesiger discloses that the water content of its water/cellulose derivative mixture must be controlled and adjusted within specific percentages based on the weight of the cellulose derivative:

The amount of water in the feed composition is chosen so as to achieve a sufficient swelling or dissolution in order to destroy the predominant structures and obtain the desired bulk density. The amount is conveniently 50 to 80 wt. %, preferably 65 to 78 wt. % and most particularly preferably 68 to 76 wt. % of water, based on the total weight of the feed composition. It has surprisingly been found that a minimum specific water content is necessary in order to achieve a desired bulk density of the ground product.

Id. at 5:59–67

Given these teachings, we agree with the Examiner that Schlesiger describes a process having all of the steps and features required by claim 1.

We acknowledge, as Appellants argue (App. Br. 9), that Schlesiger does not expressly state that, by including a predetermined amount of water in its water/cellulose derivative mixture, and thereby controlling and adjusting the water content of that mixture, the release rate of the active ingredient ultimately combined with the dry-ground cellulose derivative will also be controlled and adjusted. We acknowledge also that Schlesiger's reason for controlling and adjusting the water content is not for Appellants' purpose of controlling the release of the active agent.

As noted above, however, Appellants' Specification discloses that when one adjusts and controls the water content in a water/cellulose derivative mixture, by including a predetermined amount of water in that mixture, one necessarily, that is inherently, also adjusts and controls the release rate of the active ingredient ultimately combined with the dry-ground cellulose derivative. *See, e.g.,* Spec. 12–16.

Accordingly, that an ordinary artisan might not have been aware that adjusting and controlling the water content, as taught by Schlesiger, also necessarily adjusts and controls the release rate of the active ingredient, does not demonstrate that Schlesiger fails to anticipate claim 1, or fails to describe that feature inherently. *See MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (“Inherency is not necessarily coterminous with knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art.”).

Contrary to Appellants' arguments (App. Br. 10), claim 1 does not require the intentional pre-selection of a desired release rate and a selection of specific diluent content in order to achieve that desired release. Thus, that

Schlesiger's process does not include those steps does not demonstrate a lack of anticipation, because claim 1 does not include those steps. Moreover, because the rejection at issue is for anticipation, we do not find Appellants' arguments regarding the application of inherency principles to the issue of obviousness persuasive. *See* Reply Br. 2–3.

In sum, for the reasons discussed, Appellants' arguments do not persuade us that a preponderance of the evidence fails to support the Examiner's finding that Schlesiger describes a process having all of the steps and features required by claim 1. We, therefore, affirm the Examiner's anticipation rejection of claim 1 over that reference. Because they were not argued separately, claims 10 and 15 fall with claim 1. *See* 37 C.F.R. § 41.37(c)(1)(iv).

Appellants persuade us, however (App. Br. 14; Reply Br. 3–4), that Schlesiger does not include claim 3's step of adjusting the diluent content to a first value using a first amount of diluent, and also adjusting to a second value using a second amount of diluent. The Examiner contends that Schlesiger's process includes that step because it is reasonable to interpret claim 3 as encompassing adjustment to the same value twice. Ans. 9. We are not persuaded.

Rather, we agree with Appellants that, given claim 3's express use of the terms "first value" and "second value" to describe the diluent amounts used in the claim, an ordinary artisan would not have considered it reasonable to interpret those values as being the same. We, therefore, reverse the Examiner's rejection of claim 3 for anticipation by Schlesiger.

OBVIOUSNESS—SUGIMOTO

In rejecting claims 1, 3, 10, and 11 for obviousness over Sugimoto, the Examiner found that Sugimoto describes a process having all of the steps and features required by the rejected claims, except that the “differences between the prior art and the claims at issue appears to be the time point at which the liquid diluent is added to the composition.” Ans. 4.

The Examiner reasoned, nonetheless, that while Sugimoto discloses adding the liquid diluent “during grinding, addition of the diluent before grinding is *prima facie* obvious. See MPEP § 2144.04(1V) (“Changes in Sequence of Adding Ingredients”). The order in which ingredients are added to a composition is routinely varied by the skilled artisan using nothing more than routine experimentation.” *Id.*

In particular, the Examiner reasoned:

For example, the equipment available to the skilled artisan may provide motivation to add ingredients in a particular order. Where the skilled artisan only has access to equipment for adding a liquid prior to grinding, one would naturally be motivated to use that equipment in the manner for which it was designed. One is motivated to use the tools at hand, and if they require addition of liquid at a particular point during manufacturing, then that is the course of action that one would be motivated to pursue. The skilled artisan may also be motivated to add liquids to powdered or dry ingredients prior to processing in order to improve material handling. For example, one may desire to add a liquid to a dry ingredient early in processing in order to form a paste and thereby avoid fines or powders that may become airborne and inhaled by manufacturing personnel. One would have had a reasonable expectation of success because changing the order in which ingredients are added to a composition is routine in the pharmaceutical arts. Finally, there are only a limited number of finite sequences or steps in which the various ingredients may

be mixed, and it is *prima facie* obvious to determine which order of steps produces the most effective manufacturing method.

Id. at 4–5 (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007)).

Appellants argue, among other things, that rather than being a simple rearrangement of the order of steps in Sugimoto, the steps in independent claim 1 are actually different from the steps of Sugimoto’s process, and are not suggested by Sugimoto. App. Br. 11–13.

We find that Appellants have the better position.

In *KSR v. Teleflex*, the Supreme Court emphasized “an expansive and flexible approach” to the obviousness question, 550 U.S. at 415, but also reaffirmed the importance of determining “whether there was an apparent reason to combine the known elements *in the fashion claimed* by the patent at issue.” *Id.* at 418 (emphasis added).

Ultimately, therefore, “[i]n determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.” *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted).

We agree with Appellants that a preponderance of the evidence does not support the Examiner’s contention that Sugimoto would have suggested performing the process recited in claim 1, in the fashion recited by the claim.

Sugimoto discloses that “that cogrinding of a poorly water-soluble drug with water-soluble polymers in the presence of small amount of water was remarkably effective to improve its apparent solubility.” Sugimoto 12. In particular, Sugimoto discloses that a “coground mixture of nifedipine

(NP)-polyethylene glycol 6000-hydroxypropylmethyl cellulose system prepared in the presence of small amount of water showed remarkable effect with respect to NP dissolution and its apparent solubility.” *Id.* at 11 (abstract).

Sugimoto teaches that grinding the cellulose derivative, drug, and water together are critical to achieving the objective of increased drug solubility:

From the results shown in Figs. 1 and 2, it was demonstrated that the cogrinding of NP with HPMC (TC-5R) [hydroxypropyl methyl cellulose] and PEG can be an effective method to improve the dissolution rate, and that this method is superior to the conventional spray drying product. In particular, cogrinding in the presence of a small amount of water found to be remarkably effective with respect to the improvement of apparent solubility and dissolution of poorly water soluble drug.

Sugimoto 15.

Given Sugimoto’s disclosure of the importance of grinding the cellulose derivative, drug, and water *together* to achieve the objective of increased drug solubility, we are not persuaded that the Examiner has adequately explained why Sugimoto would have led an ordinary artisan to, instead, first grind the cellulose derivative and water, in the absence of the drug, and then combine the drug with the ground cellulose product, as required by claim 1. Moreover, given the criticality of grinding the cellulose derivative, drug, and water together to achieve the objective of increased drug solubility, we are not persuaded that an ordinary artisan viewing Sugimoto would have considered the order of combining the ingredients to be arbitrary, as the Examiner suggests. Accordingly, we reverse the

Examiner's rejection of claim 1, and its dependent claims 3, 10, and 11, for obviousness over Sugimoto.

OBVIOUSNESS—SCHLESIGER AND WEBER

In rejecting claims 1 and 9 for obviousness over Schlesiger and Weber, the Examiner relied on the teachings in Schlesiger, discussed above in relation to claim 1, and cited Weber as evidence that it would have been obvious to control the amount of diluent used in Schlesiger's process by separating the diluent from the polysaccharide, as recited in claim 9, which depends from claim 1. Ans. 5–6.

Appellants do not contend that the Examiner erred in concluding that an ordinary artisan would have considered it obvious to combine the teachings of Weber and Schlesiger, in the manner posited as suggesting the process recited in claim 9. Rather, Appellants assert that the combination of references fails to teach or suggest all the features of claim 1. *See App. Br.* 11–12.

For the reasons discussed above, however, Appellants do not persuade us that Schlesiger fails to describe a process having all of the steps and features of claim 1. Therefore, because Appellants do not identify, nor do we discern, any deficiency in the Examiner's conclusion of obviousness as to claims 1 and 9 over Schlesiger and Weber, we affirm the Examiner's rejection of those claims over those references.

**OBVIOUSNESS—SCHLESIGER
OR SUGIMOTO COMBINED WITH ANDREWS**

In rejecting claims 1 and 16 for obviousness over either Sugimoto or Schlesiger in combination with Andrews, the Examiner relied on the teachings in Schlesiger and Sugimoto, discussed above in relation to claim 1,

and cited Andrews as evidence that it would have been obvious to granulate the ground polysaccharide of either Schlesiger or Sugimoto before incorporating it into a dosage form, as recited in Appellants' claim 16, which depends from claim 1. Ans. 6–7.

Appellants do not contend that the Examiner erred in concluding that an ordinary artisan would have considered it obvious to combine the teachings of Andrews and Schlesiger, in the manner posited as suggesting the process recited in claim 16. Rather, Appellants assert that the combination of references fails to teach or suggest all the features of claim 1. *See App. Br.* 11–12.

For the reasons discussed above, however, Appellants do not persuade us that Schlesiger fails to describe a process having all of the steps and features of claim 1. Therefore, because Appellants do not identify, nor do we discern, any deficiency in the Examiner's conclusion of obviousness as to claims 1 and 16 over Schlesiger and Andrews, we affirm the Examiner's rejection of those claims over those references.

As to the alternative rejection based on Sugimoto, however, the Examiner does not persuade us, for the reasons discussed above, that Sugimoto would have rendered obvious the process recited in claim 1. Because the Examiner does not rely on Andrews for any teachings that remedy above-discussed the deficiencies of Sugimoto in relation to claim 1, and because we discern no such teachings, we reverse the Examiner's rejection of claims 1 and 16 over Sugimoto and Andrews.

SUMMARY

We affirm the Examiner's rejection of claims 1, 10, and 15, under 35 U.S.C. § 102(b), as anticipated by Schlesiger.

We reverse the Examiner's rejection of claim 3, under 35 U.S.C. § 102(b), as anticipated by Schlesiger, however.

We reverse the Examiner's rejection of claims 1, 3, 10, and 11, under 35 U.S.C. 103(a), for obviousness over Sugimoto.

We affirm the Examiner's rejection of claims 1 and 9, under 35 U.S.C. § 103(a), for obviousness over Schlesiger and Weber.

We affirm the Examiner's rejection of claims 1 and 16, under 35 U.S.C. § 103(a), for obviousness over Schlesiger in combination with Andrews.

We reverse the Examiner's rejection of claims 1 and 16, under 35 U.S.C. § 103(a), for obviousness over Sugimoto in combination with Andrews.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART